43. (New) The method of claim 42 wherein the mammal is a mouse.

Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 2 and 17 are amended, and claims 41-43 are added. Claims 1-13, 16-18, 31, 34-39, and 41-43 are pending.

Support for the amendment to claims 1, 2 and 17 can be found in the originally-filed claims 1, 2 and 17. The amendment to claims 1, 2 and 17, to delete the phrase "a variant thereof", is not intended to limit the scope of equivalents to which any claim element may be entitled.

Support for new claim 41 is found in originally-filed claims 5 and 12. Support for new claims 42-43 is found in Example I and throughout the specification.

With respect to items 1 and 4 on page 2 of the Office Action, the Examiner is requested to note that the "Cross-Reference to Related Application" section of the present application was deleted in the Amendment filed on August 17, 1999.

The Examiner rejected claims 1-13, 16-18, 31, and 34-39 under 35 U.S.C. § 112, first paragraph. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

In particular, the Examiner asserts that the specification, while being enabling for treating experimental autoimmune myasthenia gravis (EAMG) in mice with acetylcholine receptor (AChR) peptides, allegedly does not reasonably provide enablement for treating humans via the nasal administration of endogenous or exogenous universal antigens.

Applicant submits that a specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the statements contained therein which are relied upon for enabling support. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

Applicant's specification provides a detailed description of *in vitro* methods employed to identify universal epitope peptides for a particular antigen (page 27, lines 9-page 28, line 27). The specification also discloses that the peptides may be identified and further characterized *in vivo*, e.g., using animal models for a particular antibody-mediated disease (page 28, line 28-page 29, line 18). Antibody-mediated diseases are disclosed as including myasthenia gravis, systemic lupus erythematosus, Graves' disease, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, primary biliary sclerosis and pernicious anemia (page 22, lines 12-16). In addition, it is disclosed that the administration of an endogenous protein, e.g., factor VIII for hemophilia A and factor IX for hemophilia B, can result in an antibody-mediated disease (page 24, line 13-page 25, line 5). Example 1 shows that the nasal administration of AChR epitope peptides to mice can tolerize these mice against EAMG. Example 2 describes that pools of factor VIII epitope peptides were used to identify regions of factor VIII that were strongly recognized by $CD4^+$ of healthy individuals, regions which are useful to prepare factor VIII universal epitope peptides. Example 2 also describes a mouse model for hemophilia A.

Thus, Applicant's specification clearly enables the identification and use of universal epitope peptides for antibody-mediated disorders other that myasthenia gravis (MG).

Moreover, the Examiner is respectfully requested to consider the Rule 132 Declaration enclosed herewith, executed by Dr. Bianca Conti-Fine, the inventor of the subject matter claimed in the above-identified application. In the Declaration, Dr. Conti-Fine states that the administration of a pool of immunodominant factor VIII peptides to a strain of mice that is an art recognized murine model of hemophilia A, resulted in a decrease in the level of anti-factor VIII antibodies. Dr. Conti-Fine also states that universal factor VIII epitope peptides were identified using CD4+ cells from hemophilia A patients, autoimmune hemophilia A patient and healthy individuals that have a CD4+ response to factor VIII. She concludes that these results, as well as those described in the above-identified application, clearly evidence that universal immunodominant epitopes are generally present on antigens and that those peptides can be used to inhibit an indication or disease associated with aberrant, pathogenic or undesirable antibody production.

The Examiner alleges that "as readily recognized by Applicant in their response of 9-5-00 page 10, first paragraph, one of skill in the peptide therapy art would not reasonably expect effective animal therapy data to translate into human therapy effectiveness", citing to Norman et al. (Am. J. Respir. Crit. Care. Med., 154, 1623 (1996)) to support the proposition that results obtained with peptides in animals is not predictive of results in humans. First, the Examiner mischaracterizes Applicant's statements in the Amendment filed on September 5, 2000. In fact, Applicant stated that *in vitro* and *in vivo* results from inbred mice obtained with a certain peptide is not predictive that the peptide has a universal epitope, i.e., it is an epitope recognized by a majority of mammals having divergent immune response loci. Even if a universal epitope peptide for a certain antigen in mice was identified, it is unlikely that the same peptide has a universal epitope for humans as the immune response loci for mice (HLA) are quite different and much less complex that the immune response loci of humans (MHC).

With respect to Norman et al., the authors relate that the subcutaneous administration of two peptides having sequences from Fel d 1 (cat dander) to humans resulted in a decrease in nose and lung symptoms, not in IgG or IgE antibody or T cell proliferation. Norman et al. note that their results were in contrast to the T cell tolerization allegedly observed after subcutaneous administration of those same peptides to inbred mice. Although the results observed in inbred mice and humans administered the same peptides were not identical, both results were indicative of a modulation of the immune response after peptide immunization. Therefore, animal data is reasonably predicative of human data.

Further, the Examiner is reminded that if one of skill in the art would accept that animal model data would correlate with that for humans, the Patent Office should also accept those data as sufficient support under § 112 for the claimed methods in humans. *See In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995); M.P.E.P. § 2164.02. Certainly, the art worker employs a particular animal model to test an agent with the reasonable expectation that the results obtained with that model correlate to results in humans.

To support the position that it would require undue experimentation by the art worker to practice endogenous peptide therapy, the Examiner cites Wraith et al. (Cell, 59, 247 (1989)) and Tisch et al. (Proc. Natl. Acad. Sci. USA, 91, 437 (1994)). Wraith et al. speculate that one of the difficulties with using a peptide which binds to a site on the major histocompatibility complex (MHC) but which does not stimulate T cells to treat autoimmune diseases is that some autoantigens have multiple distinct epitopes represented by different MHC class II molecules and that inhibition of one class II molecule may lead to escape to an autoimmune response to a separate epitope restricted by a different class II molecule (page 253). However, in the Declaration enclosed herewith, Dr. Conti-Fine states that the administration of a universal epitope peptide for antibody-mediated disorders does not necessarily lead to deletion of peptide-specific T cells but does lead to stimulation of modulatory T cells. These modulatory T cells (e.g., Th2 and Th3) exert their suppressive action on an antibody-mediated immune response by virtue of the regulatory cytokines that they secrete (paragraph 10 of the Declaration). Those cytokines inhibit the activity of any pathogenic immune cells in their proximity, irrespective of their epitope specificity, or even antigen specificity (antigen-mediated bystander suppression) (paragraph 10 of the Declaration). Dr. Conti-Fine also states that this protective mechanism is quite different from those of epitope-specific immunosuppressive approaches that act through direct deletion of pathogenic T cells. Those approaches require the use of a most comprehensive pool of epitopes and potential epitopes, and they stand the chance of being ultimately ineffective because of the emergence of new epitope specificities (paragraph 10 of the Declaration).

The Examiner points to Tisch et al. as showing that treating an ongoing immune T cell mediated immune response may have an immunizing effect and exacerbate the disease condition. Nevertheless, Tisch et al. note that how an antigen is administered is a factor in determining whether an immunogenic or tolerogenic response is induced (page 437). In this regard, Tisch et al. indicate that oral and nasal administration of antigen or antigenic peptide has been successful in down-regulating self-reactive T cells (page 438).

And although Tisch et al. disclose that it is possible that the administration of an antigen/peptide after pathogenic T cells have been activated may have an immunizing effect and exacerbate the disease condition (page 437), the Examiner is requested to consider that such a response was observed in EAE, a model for a T cell mediated autoimmune disease, where intraperitoneal administration of a full length antigen was used (see page 2 of Applicant's specification). In contrast to T cell mediated immune disorders, most pathogenic antibodies in antibody-mediated immune disorders do not recognize a peptide of the cognate antigen because the peptide does not have the tertiary structure of the same sequence in the antigen (see Conti-Fine and Lei, Ann. Rev. Biophys. Biomol. Structure, 25, 197 (1996), a copy of which is enclosed for the Examiner's convenience). Karachunski et al. (J. Neuroimmunology, 93, 108 (1999), a copy of which is enclosed for the Examiner's convenience) disclose that the long term (36 weeks) subcutaneous administration of an epitope peptide or a pool of epitope peptides of AChR to mice after the appearance of EAMG did not result in the synthesis of pathogenic auto-antibodies or worsening of disease. Thus, even if antibodies are synthesized as a result of peptide administration, they do not cross-react with the antigen.

With respect to evidence that the administration of a peptide can inhibit an ongoing antibody-mediated immune response, the Examiner's attention is directed to Wu et al. (J. Immunol., 159, 3016 (1997)) and Im et al. (J. Clin. Invest., 104, 1723 (1999) (a copy of the latter two documents is enclosed herewith). These three documents report that the oral administration of a portion of AChR or parenteral administration of a peptide of AChR after induction of EAMG resulted in an improvement in EAMG.

Hence, none of the documents put forth by the Examiner support the proposition that it would require undue experimentation by the art worker to practice Applicant's invention.

The Examiner further alleges that Applicant has not enabled the term "variant". As amended, the claims no longer recite the term "variant" thereby rendering this rejection moot.

Hence, the rejection under 35 U.S.C. § 112, first paragraph, is not supported by the facts of this case, and so reversal of the §112, first paragraph, rejection and allowance of the claims is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6959) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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By her Representatives,

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Date June 1, 2001 By _____
Janet E. Embretson
Reg. No. 39,665

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX AF, Assistant Commissioner for Patents, Washington, D.C. 20231, on this 1st day of June, 2000.

Dawn M. Poole
Name

Dawn M. Poole
Signature

OIPE JC152 JUN 04 2001 PATENT & TRADEMARK OFFICE

Clean Version of Pending Claims

METHODS TO TREAT UNDESIRABLE IMMUNE RESPONSES
Applicant: Bianca M. Conti-Fine
Serial No.: 08/991,143

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1. (Thrice amended) A method of preventing or inhibiting an indication or disease associated with aberrant, pathogenic or undesirable antibody production which is specific for a particular endogenous antigen, comprising: administering to the respiratory tract of a human afflicted with, or at risk of, the indication or disease a dosage form comprising an amount of at least one epitope peptide, or a combination thereof, wherein the administration of the dosage form is effective to alter the aberrant, pathogenic or undesirable antibody production in humans having divergent HLA haplotypes, wherein the sequence of the epitope peptide comprises a universal, immunodominant epitope, and wherein the peptide comprises less than the sequence of the endogenous antigen.

2. (Thrice amended) A method of suppressing, tolerizing or inhibiting the priming or activity of $CD4^+$ T cells which are associated with antibody production specific for a particular antigen, comprising: administering to the respiratory tract of a mammal afflicted with, or at risk of, the indication or disease a dosage form comprising an amount of at least one epitope peptide, or a combination thereof, wherein the administration of the dosage form is effective to suppress, tolerize or inhibit the priming or activity of, $CD4^+$ T cells which are associated with antibody production, in mammals having divergent immune response haplotypes, wherein the $CD4^+$ T cells are specific for the antigen, wherein the sequence of the epitope peptide comprises a universal, immunodominant epitope sequence, and wherein the peptide comprises less than the sequence of the antigen.

3. The method of claim 1 wherein the administration is effective to reduce or inhibit the amount of said antibody for an antigen comprising said peptide.

4. The method of claim 2 wherein the antigen is an endogenous antigen.

5. The method of claim 4 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX

6. The method 2 wherein the antigen is an exogenous antigen.

7. The method of claim 6 wherein the exogenous antigen is a fungal antigen.

8. The method of claim 2 wherein the administration is effective to reduce or inhibit the amount of said antibody for an antigen comprising said peptide.

9. The method of claim 8 wherein the antigen is an exogenous antigen.

10. The method of claim 9 wherein the exogenous antigen is a fungal antigen.

11. The method of claim 8 wherein the antigen is an endogenous antigen.

12. The method of claim 11 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

13. The method of claim 2 wherein the mammal is a human.

16. The method of claim 2 wherein the antigen is an exogenous antigen from a domestic cat.

17. (Thrice amended) A method to tolerize a human to an endogenous antigen associated with aberrant, pathogenic or undesirable antibody production in the human, comprising: administering to the respiratory tract of the human at least one epitope peptide, or a combination thereof, having a universal immunodominant epitope sequence, wherein the administration is effective to tolerize $CD4^+$ cells which are associated with antibody production, in humans having divergent HLA haplotypes to the endogenous antigen and wherein the peptide comprises less than the sequence of the antigen.

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18. The method of claim 17 wherein the peptide is nasally administered.

31. The method of claim 1, 2, or 17 wherein the administration does not increase synthesis of pathogenic antibody to the native antigen.

34. The method of claim 1 or 2 wherein the administration is effective to reduce or inhibit the affinity of the antibody for an antigen comprising said peptide.

35. The method of claim 34 wherein the antigen is an endogenous antigen.

36. The method of claim 35 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

37. The method of claim 34 wherein the antigen is an exogenous antigen.

38. The method of claim 37 wherein the antigen is a fungal antigen.

39. The method of claim 1, 2 or 17 further comprising administering an agent that inhibits B cell activation.

41. (New) The method of claim 17 wherein the endogenous antigen is the acetylcholine receptor, insulin, growth hormone, factor VIII or factor IX.

42. (New) The method of claim 2 wherein the peptide includes residues 150-169, 181-200 or 360-378 of the *Torpedo californica* acetylcholine receptor alpha subunit or a portion of those residues.

43. (New) The method of claim 42 wherein the mammal is a mouse.